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Associations between human exposure to polybrominated diphenyl ether flame retardants via diet and indoor dust, and internal dose: A systematic review

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The aim of this review was to identify and appraise the current international evidence of associations between concentrations of polybrominated diphenyl ethers (PBDEs) in humans and their indoor dusts and food. We systematically searched Medline, Embase, Web of Science and Scopus (up to Jan 2015), using a comprehensive list of keywords, for English-language studies published in peer-reviewed journals. We extracted information on study design, quality, participants, sample collection methods, adjustments for potential confounders and correlations between PBDE concentrations in internal and external matrices. Of 131 potential articles, 17 studies met the inclusion criteria and were included in the narrative synthesis. We concluded that three key factors influenced correlations between external and internal PBDE exposure; half-life of individual congeners in the human body; proximity and interaction between PBDE source and study subject; and time of study relative to phase out of PBDE technical products. Internal dose of Penta-BDE technical mix congeners generally correlated strongly with dust. The exception was BDE-153 which is known to have higher persistence in human tissues. Despite the low bioaccessibility and short half-life of BDE-209, its high loading in dusts gave strong correlations with body burden where measured. Correlations between PBDE concentrations in duplicate diet and body burden were not apparent from the included studies. Whether dust or diet is the primary exposure source for an individual is tied to the loading of PBDE in dust or food items and the amounts ingested. Simple recommendations such as more frequent hand washing may reduce PBDE body burden.

1. Introduction

Polybrominated diphenyl ethers (PBDEs) are a class of brominated flame retardant, which have been widely used to meet fire safety regulations for fabrics, furnishings, electronics and vehicles since the 1970s. PBDEs are additive flame retardants, meaning that they are mixed into plastics or foam without forming chemical bonds. Fabrics and textiles can also be treated with PBDE commercial mixtures to provide protection. During the lifetime of products, PBDEs can leach out, thus becoming ubiquitous in indoor air and dust (Harrad et al., 2010). From there they migrate further into the wider environment and bioaccumulate through food chains (Harrad and Diamond, 2006). The human body burden of PBDEs increased dramatically from the 1970s until the 1990s (Frederiksen et al., 2009b; Hites, 2004; Meironyte et al., 1999) reflecting both wide use and persistence of these lipophilic chemicals. It is likely that regulations restricting PBDE use, e.g. Directives 2002/95/EC and 2003/11/EC and EC Designation 2008/C116/4, have been instrumental in reducing human exposure (Frederiksen et al., 2009b). However, the effects of such measures are slow to impact on levels found as contaminants in human tissue. Furthermore, recovery and recycling of electronics, particularly where unregulated in developing countries, is an additional new source of exposure (Athanasiadou et al., 2008; Ionas et al., 2014; Labunska et al., 2014; Liu et al., 2008). Potential adverse human health effects of PBDE exposure and body burden are well documented and include reproductive toxicity, neurotoxicity, endocrine activity, DNA damage and immune effects (EFSA, 2011; Kim et al., 2014; Linares et al., 2015; Lyche et al., 2015; US-EPA, 2010). The bioaccessibility of ingested PBDEs has been estimated to be 32-60% for tri- to hepta-BDEs, and 14-25% for deca-BDE (Abdallah et al., 2012; Fang and Stapleton, 2014). PBDE bioaccessibility generally decreases with increasing octanol-water partitioning coefficient (Log K_{ow}) a measure of relative solubility in lipid and water (Abdallah et al., 2012; Fang and Stapleton, 2014). It is widely accepted that PBDEs can have

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substantial half-lives in humans. There is a general trend of shorter half-lives for the higher brominated compounds, with estimates of residence time for BDE-209 of just a few days, and for main congeners of the technical Penta-BDE mixture (i.e. BDE-47, -99, -100) around two to four years (Geyer et al., 2004; Thuresson et al., 2006). Over the last few years, a number of studies have investigated matched internal and external PBDE exposure. A thorough review of such studies may reveal common patterns, which may generate recommendations for reducing exposure and identify future research needs. This new evidence will help to determine whether external exposure measurements can be used as indicators of human internal PBDE exposure. The aims of this systematic review were: (1) to identify, appraise and summarise the current international literature on the association between PBDE concentrations measured in food items and indoor dusts with human body burdens; and (2) to determine the relative contributions made by indoor dust ingestion and dietary exposure to PBDE body burden for general non-occupational human exposure.

2. Methods

2.1. Literature search and selection criteria

The process of this review followed the guidance for conducting systematic reviews from the Centre for Reviews and Dissemination (CRD, 2009) and 'Preferred Reporting Items for Systematic Reviews' guidelines (Moher et al., 2009). Papers were identified through searches of the environmental and medical literature databases (Medline, Embase, Web of Science, Scopus) using relevant terms for PBDEs, internal dose, external exposure and matched exposure. The Boolean operators 'AND' and 'OR' were used to combine topic areas; i.e. ($bde OR pbde OR pbdes OR (polybrominated and ('diphenyl' de OR diphenyl) and ('ethers' de OR ethers))) AND (serum$ OR plasma$ OR blood$ or milk$ OR internal OR body burden$ OR exposure$) AND (diet$ OR food$ OR dust$ OR air$ OR indoor$ OR environment$ OR exposure$ OR factor$ OR lifestyle$ OR source$ OR behav$) AND (match$ OR pair$ OR relation$ OR association$ OR evidence$ OR predict$). A comprehensive description of the search strategy is available in SI1. Reference lists of the identified published studies were also scanned and experts in the field were consulted.

Studies were included if they met the following inclusion criteria: a) explored correlations in PBDE concentrations between paired human internal dose (serum or milk) and indoor house dust, and/or correlations between paired human internal dose (serum or milk) and diet, b) were published in the English language, c) were full original papers which were published in a peer-reviewed journal available either on-line or from the British Library. Databases were searched for papers published between 1974 to January 2015. There were no limits on the year of publication (up until Jan 2015) or the age of study participants. Studies were not included if the dust exposure measurement was purely occupational or from a hobby.

One reviewer (LB) scanned through all abstracts after the initial article selection and excluded only obvious non-eligible studies. A second reviewer scanned titles and abstracts of a 15% sample of the identified studies and confirmed decisions on inclusion. A sample of the papers that met the inclusion criteria (20%) were formally reviewed by two independent reviewers using a data extraction form modified from Glinianaia et al. (Glinianaia et al., 2004). Data extracted included information on study design, sample descriptors and collection methods, analytical and statistical methods, confounders and correlations. Concentrations of PBDE in human serum or milk (lipid weight) were used to indicate internal dose. Concentrations of PBDE in indoor dusts or in duplicate diets (per body weight) were used as the indicators of exposure. The correlations calculated for pairs of internal dose and exposures were explored.

We present a narrative synthesis of the data, as a formal meta-analysis was not possible given the heterogeneity of samples, particularly differences in: a) fire prevention regulations and technical product usage between countries (and between states in the USA); b) sample collection methods; c) congeners analysed and reported; and d) analysis and reporting of correlations between internal and external exposures.

2.2. Study quality

The quality data extraction form was based on that used by Roth and Wilks (2014) and 'Harmonization of Neurodevelopmental Environmental Epidemiology Studies' (HONEES) criteria (Youngstrom et al., 2011). Quality assessment evaluated study design (description of setting, location, data collection dates, study size), study population and sampling (eligibility criteria, recruitment methods, response rate, participant description, representation of population to whom results would be generalised), variables for adjustment (discussion of and accounting for confounders and bias), data measurement (methods of measurement, quality controls, fit with literature) and outcome measurement (statistical methods and description). Laboratory measurement quality considerations included ^{13}C internal standardisation coupled with GC-HRMS measurement, and the successful use of regular procedure blanks and reference materials. Studies were classified, regarding provision of this information, as: yes (1), no or unclear (0), or partially (0.5). Based on these criteria, three quality groups were formed: scores of 10–12 were rated high, 4–9 moderate and 0–3 low. When drawing conclusions, studies with a low quality score were given less weight. Throughout the review process we referred to recommendations from 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines (von Elm et al., 2007).

3. Results

A flow diagram of numbers of articles identified by the literature searches, screened, assessed for eligibility and included in the review, with reasons for exclusion at each stage is presented in Fig. 1. Database searches elicited 408 articles. A title and abstract review resulted in 131 original peer reviewed papers. The abstracts and, where necessary, full articles were reviewed in detail resulting in further exclusions. Twenty-three articles were included in the systematic review, concerning 17 studies which met our inclusion criteria and were included in the narrative synthesis (Fig. 1). For six of these studies, key information was extracted from additional papers to those containing the correlation analysis. The additional papers are referred to in Tables 1 and 2.

3.1. Participant characteristics and study methods

A summary of study designs, participant characteristics, sampling methods, adjustments for confounders and quality assessment for the 17 included studies is presented in Table 1. Seven of the studies took place in Europe — predominantly Scandinavia and Northern Europe, six studies took place in the USA, three took place in Australasia, and one in South Central Asia. The specific countries where the studies were conducted are included in Table 1. Only one study stated its design, this was a convenience cross-sectional sample, (Watkins et al., 2012) so recruitment information was used to deduce design for the other studies where possible. Samples recruited from a previous study's cohort or by word-of-mouth appeared to be on the basis of convenience (Coakley et al., 2013; Imm et al., 2009; Sahlström et al., 2015; Stasinska et al., 2014; Toms et al., 2009; Whitehead et al., 2015). Where participants were recruited because they were pregnant or were undergoing medical treatment, the design appeared to be prospective (Frederiksen et al., 2010; Wu et al., 2007). If recruitment was based on specific businesses or accommodation, the studies were considered to be retrospective (Ali et al., 2014; Roosens et al., 2009). Remaining studies were classed cross-sectional (Bjorklund et al., 2012; Cequier et al., 2015; Fromme et al., 2009; Johnson et al., 2010; Stapleton et al., 2012) or of unclear design (Karlsson et al., 2007).

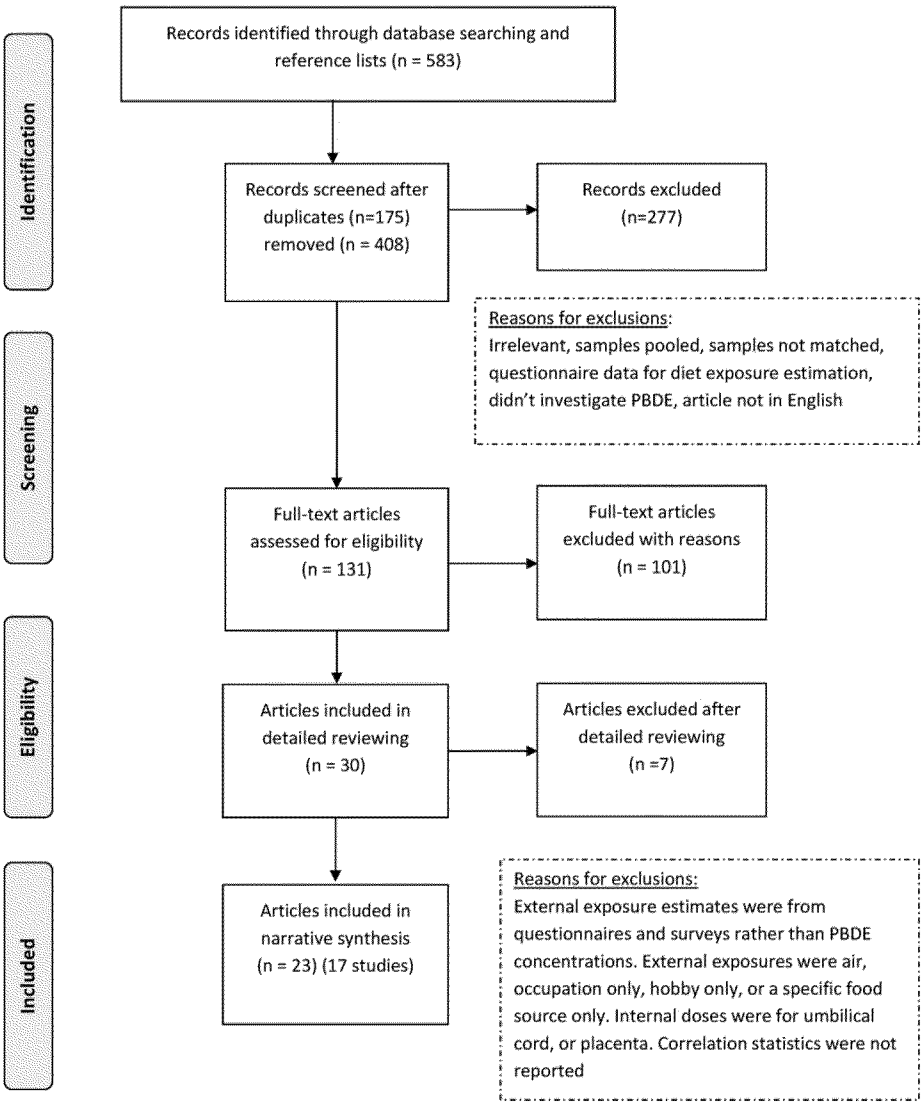

Fig. 1. PRISMA flow diagram of numbers of studies identified by the literature searches, screened, assessed for eligibility and included in the review

All studies were published from 2007 to 2015, and samples were collected between 2004 and 2012. Dates and details on participants' gender and ages, and sampling strategies for individual studies, are provided in Table 1. Thirteen studies used blood as the internal dose measure and four used breastmilk. All studies measured indoor dust, twelve collected information on dietary habits and two measured duplicate diet samples. Nine of the studies exclusively sampled women. The majority of studies involved women of reproductive age. Mixed male and female studies generally had wider age ranges, except for one study where subjects were students aged 20–25 years (Roosens et al., 2009) and another of toddlers aged 12–36 months (Stapleton et al., 2012). Where human milk was used as the measure of internal dose, participants were usually primiparous breastfeeding women (Bjorklund et al., 2012; Coakley et al., 2013; Wu et al., 2007) but not exclusively (Toms et al., 2009). Where reported, milk samples included studies that ranged in duration from: (i) 14–21 days (Bjorklund et al., 2012); (ii) 2–8 weeks (Wu et al., 2007); and (iii) 2–11 months postpartum (Toms et al., 2009).

There are no standard procedures for dust collection. The simplest dust sampling method used was to take a sample from a vacuum cleaner dust bag (VCBD) from the home which was used for seven of the studies. Where dusts were collected directly by the researcher, different areas and surfaces were sampled, sometimes including vehicles and workplaces and different rooms separately (Ali et al., 2014; Watkins et al., 2012). These aimed to maximise the likelihood of detecting differentials. Rooms were generally selected on the basis that it was the room(s) that the participant spent most time in, for example, the child or student's room (Roosens et al., 2009; Stapleton et al., 2012), the main living area (Cequier et al., 2015), the most commonly used rooms (Wu et al., 2007) or the living room and bedroom combined (Karlsson et al., 2007).

The two studies that included both dust and diet measurements estimated the proportion of internal dose attributable to each. Roosens et al. (2009) compared PBDE exposure from food intake and dust ingestion using average and high dust ingestion rates from Jones-Otazo et al. (2005). Fromme et al. (2009) used Lorber's simple one-compartment toxicokinetic model (Lorber, 2008) with ingestion, inhalation, absorption bioavailability and half-life estimations. Studies investigating the strength of different sources as predictors of body burden used multivariate regression models (Stapleton et al., 2012; Watkins et al., 2012).

3.2. Study findings

3.2.1. Major congeners reported in each matrix

Table 2 provides a summary of major congener concentrations for each measured sample matrix reported. Figs. 2 and 3 provide an

Table 1
Summary of study designs, participant characteristics, sampling methods, adjustments for confounders and quality assessment (presented in alphabetical order)

Study reference(s)	Country, data collection period, sample number, gender and age	Study design, paired sample size and recruitment details	Matrices measured for dose and exposure assessment, timing of collection	Additional information collected	Adjustments made for confounders	Quality score
1. Ali et al. (2014)	Pakistan 2011 n = 61 M & F 17–55 years	Recruited from clothing stores (n = 15), university rooms/office (n = 16) and electronics stores (n = 30)	Blood (fasted), 7–8 ml collected, serum analysed, Dust swept from 4–8 m^2 of floor of store or university hostel rooms/office, sieved b500 μm Both samples collected within one month	Age, gender, occupational history, details of electronics, foam chairs and date of last cleaning	None	Moderate
2. Bjorklund et al. (2012)	Sweden 2008 n = 18 F –	Primiparous, Swedish born, random selection from a hospital birth registry, even distribution throughout year	Milk collected 14–21 days postpartum, 35 g extracted for analysis Dust (house) VCBD and RCD (from main living area) sieved b500 μm, 10–174 mg extracted Both samples collected within one week	Age, height, weight before pregnancy, birth weight of the child, weight change during and after pregnancy, education, smoking and dietary habits	None	High
3. Cequier et al. (2014a, 2015)[a]	Norway 2012 n = 46 F –	Mother child cohort recruited through two primary schools	Blood 10 ml collected, serum analysed Dust (house) from entire living room floor Timing not reported	Dietary habits, demographic information and household factors	None	Moderate
4. Coakley et al. (2013)	New Zealand 2007–2010 n = 33 F 20–31 years	Primiparous mothers that had provided milk for 4th WHO POPS in milk survey	Milk average 250 ml collected, 2nd and 3rd months postpartum Dust (house) from 1–4 m^2 of floor in living room sitting area, vacuumed for 2–4 min Dust (mattress) n = 16 Timing not reported	Demographics and household contents	None	Moderate
5. Frederiksen et al. (2009a, 2010)[a], Vorkamp et al. (2011)	Denmark 2007 n = 51 F –	Underwent scheduled caesarean section	Blood collected during procedure, plasma analysed Dust (house) VCBD collected before and after delivery, sieved b75 μm + maternal plasma (and umbilical cord plasma). Air and VCBD pre and post delivery	Lifestyle and dietary habits information, umbilical cord plasma and pooled milk samples also analysed	None	Moderate
6. Fromme et al. (2007, 2009)[a]	Germany 2005 n = 61 M&F 15–56 years	34 households, 27 F (age 14–60 years) and 23 M (age 15–56 years) with no occupational exposure, part of INES study	Blood 30 g collected, serum analysed Duplicate diet 7 days, 30 g extracted for analysis Dust (house) VCBD, sieved b2 mm, 1 g extracted and analysed Serum samples collected during the diet collection week	Sociodemographic characteristics, living conditions, building characteristics, possible sources of contaminants, dietary habits[a]	None	Moderate
7. Imm et al. (2009)[a]	USA 2008 n = 44 M & F 43–77 years	38 households from existing cohort of Great Lakes frequent and infrequent consumers of sport fish	Blood 15–20 ml collected Dust (house) VCBD, sieved b1 mm Dusts collected prior to blood sample collection	XRF measurements of BR content of individual items in the home, demographics, dietary habits, hobbies with plastics, foam or fabrics, work environments	None	Moderate
8. Johnson et al. (2010)	USA 2007–8 n = 24 M & F –	12 couples seeking fertility treatment	Blood 5 ml collected, serum analysed Dust (house) VCBD, sieved b150 μm, Both samples collected on same day	Demographics, dietary habits, home age, heating type, system used; hours of TV and computer use; primary vehicle and hours of use; boat use; hobbies using plastic, foam, or fabric; and work environment	None	Moderate
9. Karlsson et al. (2007)[a]	Sweden – n = 5 – –	Non-occupationally exposed sample living in same home ≥5 years	Blood 10 ml collected, plasma analysed Dust (house) living room and bedroom floors and furniture, 1–2 g collected Samples taken on same day	Number of electronic devices, living area size, floor material	None	Low
10. Roosens et al. (2009)	Belgium 2007 n = 19 M & F 20–25 years	Residents of Belgium since childhood; living at the same college for 3 years	Blood 10 ml collected plasma analysed Duplicate diet 7 days Dust from students room floor, 4 m^2 or bare floor vacuumed for 4 min, sieved b500 μm, Dust and bloods collected on last day of duplicate diet	Home location, furnishings, electronics/electric appliances and lifestyle such as smoking and transportation	None	Moderate
11. Sahlstrom et al. (2014, 2015)	Sweden 2009–10 n = 20 F	First time mothers with toddlers aged 11 months already participating in POPUP study	Blood collected, 0.5–5 g serum analysed Dust (house) 1 m above the floor in the living room, kitchen, bedroom and/or hall-way	Dietary habits	None	Moderate

(continued on next page)

Table 1 (continued)

Study reference(s)	Country, data collection period, sample number, gender and age	Study design, paired sample size and recruitment details	Matrices measured for dose and exposure assessment, timing of collection	Additional information collected	Adjustments made for confounders	Quality score
	24–40 years		Samples taken on same day			
12. Stapleton et al. (2012)	USA 2009–10 n = 77 M & F 12–36 months	Children with no prior diagnosis of thyroid problems recruited via paediatric clinic patient lists	Blood 4 ml collected, serum analysed Dust (house) entire floor-surface of room in which child spent most active time, sieved b500 μm, collected during the same visit (except nine bloods collected at clinic) Handwipes also collected during same visit	Short questionnaire about the child and parents' education levels, child's length of time breastfed, ethnicity and time away from home	Children's sex, age race, parents' education levels, duration of breast-feeding, time children spent away from home, dust concentrations, and handwipe levels	High
13. Stasinska et al. (2013, 2014)	Australia 2009–11 n = 29 F ≥18 years	Pregnant women (38 weeks gestation) from the AMETS cross-sectional study	Blood 6 ml collected, plasma analysed Dust (house) VCBD 20 g, home, sieved b600 μm, Participants brought dust sample when attending clinic for blood sample collection	Demographics, anthropogenics, occupational history, medical history, smoking, home type and age, number and age of electronics, dietary habits, pregnancy, weight gain and infant anthropometrics	None	Moderate
14. Toms et al. (2009)[a]	Australia 2007–8 n = 10 F 27–40 years	Breast-feeding mothers (2–11 months postpartum) by word-of-mouth	Milk 100 ml collected between 2–11 months postpartum Dust (house) floor dust from one floor of house, sieved b2 mm Most pairs sampled within 1 month	Dietary habits, demographics, house characteristics, daily time spent on computer and in car	None	Moderate
15. Watkins et al. (2012)	USA 2009 n = 31 M&F –	Convenience & cross-sectional sample of non-smoking, adult workers, in good health, spending ≥20 h/week in an office	Blood 10 ml collected, serum analysed Dusts (house & office) entire floor and surface area of main living area, bedroom and office vacuumed 10 min, sieved b500 μm Handwipes at work ≥60 min since last hand wash, all matrices collected in same week, serums at end of work week	Dietary habits, personal habits, average hours at work, vehicle use, handwashing, dust from vehicles also analysed	None	High
16. Whitehead et al. (2013, 2015)	USA 2006–7 n = 48 F –	Mothers of children aged 0–7 years in CCLS study	Blood, serum analysed Dusts (house) VCBD, sieved b150 μm Up to five months between paired sample collections	Demographics, anthropometrics, dietary habits (modified Block FFQ) geographical, residential, sources of PBDE in the home	Hispanic ethnicity, country of origin, household annual income	High
17. Wu et al. (2007)	USA 2004–5 n = 11 F ≥18 years	First time mothers via an obstetrics office and maternity centre, living in same home ≥3 years	Milk 50 ml collected between 2–8 weeks postpartum Dusts (house) researcher collected, surface area recorded, sieved b125 μm as soon after milk as was convenient for participants (1–43 days)	Health, residential history, electronic products, foam furniture, pre-pregnancy diet, occupational history, hobbies, home renovation, and transportation	Multiple regression used to adjust for potential confounding by dietary (meat, fish and dairy) or personal factors	High

For left censored data (values below LOD/LOQ/MLD) in statistical analysis studies 3, 4, 6, 8, 15 and 13 used LOQ□0.5, studies 2, 11 and 16 used LOQ/√2, studies 1 and 10 used LOQ□fraction above LOD and studies 5 and 7 used only values above LOQ.
For correlation, studies 1, 3, 5, 6, 7 and 8 used Spearman's rank correlation for non-parametric data and studies 2, 4, 13, 15, 16 and 17 reported log or ln transformed data to enable use of Pearson's correlation for normally distributed datasets.
For quality control, studies 1, 2, 3, 4, 11, 13 and 17 reported using NIST SRM 2585 for indoor dust, study 10 used NIST SRM 2584 for house dust, study 16 used NIST SRM for serum, studies 5, 11 and 12 took part in AMAP Ring inter-laboratory tests for POPs in serum, study 17 took part in QUASIMEME inter-laboratory testing. Studies 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 15 and 16 reported subtracting method blanks. Studies 1, 2, 4, 5, 6, 9, 10, 11, 12, 14, 16 and 17 reported using ^{13}C labelled standard for BDE-209.
M: male.
F: female.
SRM: standard reference material.
NIST: National Institute of Standards and Technology — US Department of Commerce.
RSD: relative standard deviation.
POPUP: Persistent Organic Pollutants in Uppsala Primiparous.
AMETS: Australian Maternal Exposure to Toxic Substances.
CCLS: California Childhood Leukaemia Study.
Block food frequency: (Block et al., 1990).
AMAP: Artic Monitoring and Testing Programme.
QUASIMEME: Community of Practice for Marine Environmental Measurements.
VCBD: Vacuum Cleaner Bag Dust.
RCD: Researcher Collected Dust.
Additional article references for Tables 1 & 2: Cequier et al. (2014a); Frederiksen et al. (2009a); Fromme et al. (2007); Mannetje et al. (2010); Sahlstrom et al. (2014); Stasinska et al. (2013); Whitehead et al. (2013).
[a] Home air PBDE concentration was also sampled in six marked studies, but this is beyond the scope of this review and therefore not presented here.

indication of relative differences between matrices and geographical regions. The four studies using human milk as a measure of internal dose reported BDE-47 and BDE-153 to be the predominant PBDE congeners. Their total concentrations and proportions varied between EU, Australasia and USA regions as might be expected based on varied national usage of PBDE flame retardants. Two studies noted a proportion of participants having higher BDE-153 than BDE-47 in milk; 20% in Australia (Toms et al., 2009) and 3% in the USA (Wu et al., 2007). BDE-209 was analysed in three of the studies, with detection rates of 24% in the USA (Wu et al., 2007), 60% in Australia (Toms et al., 2009) and 97% in New Zealand (Coakley et al., 2013). Variation in methods and improvements in limits of detection for BDE-209 for these studies (0.1–1.0, 0.3 and 0.065 ng/g respectively) can be expected to have influenced detection rates.

BDE-47 was the major congener in blood (making up 45-100% of the total serum PBDE) in earlier studies (Karlsson et al., 2007) and in the USA and Australia where penta-BDE technical mix (e.g. DE-71) was more heavily used and phased out more recently (Imm et al., 2009; Johnson et al., 2010; Stapleton et al., 2012; Stasinska et al., 2014). BDE-153 was the major congener in blood in Denmark, Germany and Belgium (Frederiksen et al., 2010; Fromme et al., 2009; Roosens et al., 2009) where penta- BDE use was lower than that in the USA and penta- and octa-BDE were banned in 2004. These findings indicate that regional PBDE regulations and use patterns, time of study relative to phase out of PBDE use and half-life of PBDE congeners are key factors in predicting internal dose of different congeners.

BDE-209 was the predominant congener in dust for almost all studies. The next most abundant congeners in dust tended to be BDEs-99, followed by -47 (Coakley et al., 2013; Fromme et al., 2009; Johnson et al., 2010; Karlsson et al., 2007; Stasinska et al., 2014). Differences in congener patterns were again noticeable between the USA and Europe, indicating the importance of regional use patterns in predicting exposure to PBDEs from dust. European studies demonstrated the highest congener percentages of BDE-209 in dust, with averages reported around 70–90% (Bjorklund et al., 2012; Fromme et al., 2009; Karlsson et al., 2007; Roosens et al., 2009). USA studies had lower BDE-209 proportions (0–60%) (Johnson et al., 2010; Wu et al., 2007) and Australia and New Zealand dust loadings appeared to be somewhere between the USA and EU, with BDE-209 making up approximately 66% of the PBDE total (Stasinska et al., 2014).

A small percentage of dust samples had greater ∑ penta-BDE concentrations in dust than BDE-209 concentrations (Frederiksen et al., 2010; Johnson et al., 2010; Wu et al., 2007) indicating a particular source within that indoor environment. Bjorklund et al. (2012) found concentrations of individual congeners were higher in samples collected from ≥1 m above flooring vs VCBD (median 2–3 times), however it is unclear whether this trend would be observed in other studies.

The major contributing PBDE congeners in the Belgian duplicate diet study were BDE-47 N -99 N -153 (Roosens et al., 2009). Major congeners in the German duplicate diets were different with a predominance of BDEs-99, -183 then -47 (Fromme et al., 2009).

3.3. Intermatrix correlations

A summary of the correlations between paired internal and external exposure measurements reported in the 17 included studies is provided in Table 2. BDE-47 in dust and internal dose measurements were significantly correlated ($p < 0.05$) in seven of the studies (including three of the four studies using milk), BDE-99 in four studies, BDE-153 in three studies and BDE-209 in only one (Coakley et al., 2013).

The strongest correlation reported was for technical Penta-BDE mix components BDE-47,-99, and -100 (∑ BDE_3) between handwipes and serum in children age 36–72 months (Stapleton et al., 2012). This finding indicates proximity between source and receptor to be a key factor in predicting strength of correlation between internal dose and exposure measurement. Also very strongly correlated were paired BDE-47 in VCBD dust and blood, particularly in American studies and older EU studies (Frederiksen et al., 2010; Johnson et al., 2010; Whitehead et al., 2015), indicating the importance of time of study relative to PBDE use phase out. Similarly strongly correlated were BDE-99 in VCBD dust and blood (Johnson et al., 2010; Whitehead et al., 2015), BDE-47 in house dust and milk (Wu et al., 2007), ∑ penta-BDEs in bedroom dust and blood (Ali et al., 2014; Watkins et al., 2012) and BDE-153 in mattress dust and serum (Coakley et al., 2013). Significant correlations between BDE-153 in dust and internal dose were also found for university hostel dust (Ali et al., 2014). These findings indicated that time spent in proximity to the PBDE source is a key factor for predicting associated internal dose. Associations between BDE-153 in children's handwipes and serum were weaker than their associations for ∑ BDE_3 (∑ BDE-47, -99, -100) (Stapleton et al., 2012), an indicator of the importance of congener half-life when predicting internal dose. BDE-153 has the longest PBDE residency time in humans, estimated to be 14-16 years (Geyer et al., 2004), leading to body burden proportions increasing over time in relation to other congeners. Where BDE-209 analysis in blood was successful, concentrations were reported to be 50% of the total PBDE body burden, indicating strong on-going exposure given its relatively short biological half-life.

Where congeners associated with particular technical mixtures were significantly correlated with each other in dust the findings were reported to indicate one or more items containing such technical mix in the area sampled (Bjorklund et al., 2012; Frederiksen et al., 2010). Coakley et al. (2013) reported strong and significant correlations between congeners from the same technical product, for Penta-BDE, Octa-BDE and Deca-BDE technical mixes, both within and between matrices, again suggesting a specific source or sources of the technical product. BDE-209 was not found to correlate with congeners in other technical mixtures indicating different sources or applications. This indication would also fit with data sets where a small percentage of dust samples had greater ∑ penta-BDE concentrations in dust than BDE-209 concentrations (Frederiksen et al., 2010; Johnson et al., 2010; Wu et al., 2007).

Thirteen studies investigated house characteristics and contents as predictors of dust or serum PBDE concentrations. Two studies reported urban home dusts had significantly higher penta-BDE than rural home dusts (Cequier et al., 2015; Coakley et al., 2013). Other home characteristics predicted dust PBDE for only one study each e.g. age of home and whether home was detached (Cequier et al., 2015), older carpet underlay (Coakley et al., 2013), number of flat screen TVs, number of TV/gaming consoles, number of DVD/video players, and number of electronics (Cequier et al., 2015). Subjects with crumbling or exposed foam in their homes were found to have higher serum levels of BDE-47 and -99 than those who did not (Whitehead et al., 2015). Imm et al. (2009) used a portable X-ray fluorescence (XRF) spectrometer to measure the bromine content in household and vehicle items and reported that Br concentrations in pillows ($r = 0.69$, $p = 0.005$) and vehicle seat cushions ($r = 0.56$, $p = 0.03$) correlated significantly with serum concentrations. When the importance of different rooms was considered, dusts from bedrooms and main living areas indicated the strongest correlations with body burden over office workplaces (Ali et al., 2014; Watkins et al., 2012). This finding highlighted the importance of time spent in locations with sources when estimating exposure. Two studies from the USA estimated the proportional impact of variants on body burden. The study of toddlers reported that handwipe levels, child's sex, child's age, and father's education accounted for 39% of the variation in serum ∑ BDE-47,-99,-100(∑ penta-BDE_3) levels, yet 39% of the variation in serum BDE 153 came from age, handwipe levels, and breastfeeding duration (Stapleton et al., 2012). Watkins et al. (2012) reported that main living area dust and handwipes predicted 55% of the variation in serum.

The studies in Germany and Belgium measuring both duplicate diet and dusts as predictors of serum PBDEs both reported dietary exposure to be the greater. Fromme et al. (2007) reported the dietary

Table 2
Total concentrations of major PBDE congeners in milk, blood, dust and duplicate diet samples and correlations between them (presented in alphabetical order).

Study, measure of external exposure	Total number of PBDE congeners analysed	BDE congener	Milk ng/g lw	Blood ng/g lw	Dust ng/g dw	Diet ng/g ww	Correlations	
			Median (range) % detect				r	p
1. Ali et al. (2014) electronic store dust	Serum — 8 Dust — 11	BDE-47	–	0.9 (b0.5–4)	3 (b0.2–365)	–	− 0.85	0.32
		BDE-99	–	0.7 (b0.4–2.8)	3 (b0.2- 345)	–	0.54	b0.01
		BDE-153	–	0.8 (b0.2–3.7)	1.2 (b0.2–150)	–	0.01	0.48
		∑ pentaPBDE	–	2.5 (0-11)	10 (1-1150)	–	0.15	0.21
		BDE-209	–	–	155 (b2–51,500)	–	–	–
Clothing store dust		BDE-47	–	0.8 (b0.5–3)	1.7 (b0.2–6.5)	–	0.07	0.4
		BDE-99	–	0.5 (b0.4–1)	2.0 (b0.2–8.8)	–	− 0.16	0.28
		BDE-153	–	0.8 (0.2–2)	0.6 (b0.2–1.5)	–	0.26	0.18
		∑ pentaPBDE	–	2.5 (0.5-5)	5 (0.8-19)	–	0.19	0.25
		BDE-209	–	–	45 (b2–195)	–	–	–
University hostel dust		BDE-47	–	1.0 (b0.5–11)	2.2 (1–12.5)	–	0.56	0.01
		BDE-99	–	0.8 (b0.4–11)	3.5 (1–23)	–	0.48	0.03
		BDE-153	–	1.1 (0.4–2.2)	1 (0.5–5)	–	0.43	0.04
		∑ pentaPBDE	–	3 (1-25)	7.5 (2.5-50)	–	0.64	b0.01
		BDE-209	–	–	65 (12–205)	–	–	–
2. Bjorklund et al. (2012) VCBD	Milk — 10 Dust — 16	BDE-47	0.85 (0.41–12) 72	–	15 (1.5–47) 100	–	0.51	0.029
		BDE-99	– (b0.16–1.4) 17	–	13 (0.074–68) 100	–	–	–
		BDE-153	0.58 (0.26–1.6) 100	–	2.2 (0.12[c]–12) 95	–	0.037	0.88
		BDE-209	–	–	280 (110–6600) 100	–	–	–
≥1 m above floor		BDE-47	–	–	38 (8.5–250) 100	–	0.281	0.109
		BDE-99	–	–	25 (2.3[c]–130) 94	–	–	–
		BDE-153	–	–	6.0 (0.96–14) 100	–	0.322	0.208
		BDE-209	–	–	520 (190–9300) 100	–	–	–
3. Cequier et al. (2014a, 2015)	Serum — 7 Dust — 9	BDE-47	–	0.49 (bLOD–11) 74	126 (NLOD–1510) 100	–	− 0.23	ns
		BDE-99	–	0.13 (bLOD–2.6) 17	171 (bLOD–2,610) 98	–	–	–
		BDE-153	–	0.82 (NLOD–5.1) 100	26.0(bLOD–254) 98	–	− 0.18	ns
		BDE-209	–	–	325 (bLOD–204,000) 98	–	–	–
		$\sum_7$PBDE	–	2.3 (NA-23)	426 (NA-5,125)[e]	–	- 0.33	b0.05
4. Coakley et al. (2013) floor dust	Milk and dust — 16	BDE-47	2.140 (0.317–7.710) 100	–	24.2 (0.3–98) 97	–	0.39	b0.05
		BDE-99	0.560 (0.0662–1.290) 100	–	31.5 (3.3–219.1) 100	–	0.33	ns
		BDE-153	0.517 (0.142–3.820) 100	–	4.6 (0.3–58.9) 88	–	0.15	ns
		BDE-209	0.1905 (0.0653–3.140) 97	–	598 (28.8–27,394) 100	–	0.37	b0.05
Mattress dust		BDE-47	2.140 (0.317–7.710) 100	–	46.3 (6.5–288.4) 100	–	0.52	b0.05
		BDE-99	0.560 (0.0662–1.290) 100	–	41.8 (8.1–540.3) 100	–	0.41	ns
		BDE-153	0.517 (0.142–3.820) 100	–	6.7 (0.3–58.2) 94	–	0.74	b0.005
		BDE-209	0.1905 (0.0653–3.140) 97	–	1018 (106 − 21,956) 100	–	0.5	b0.05
5. Frederiksen et al. (2009a, 2010), Vorkamp et al. (2011) VCBD before delivery	Serum and dust — 11	BDE-47	–	0.38 (b0.011–7.88) 80	16.9 (3.29 − 962) 100	–	0.52	0.0006
		BDE-99	–	0.11 (b0.053–18.5) 37	13.6 (2.72 − 1,764) 100	–	0.36	0.1372
		BDE-153	–	1.13 (b0.013–36.0) 98	2.48 (0.547 − 182) 100	–	0.11	0.462
		BDE-209	–	1.71	332	–	0.49	0.062

Table 2 (continued)

Study, measure of external exposure	Total number of PBDE congeners analysed	BDE congener	Milk ng/g lw	Blood ng/g lw	Dust ng/g dw	Diet ng/g ww	Correlations	
			Median (range) % detect				r	p
				(b0.66–3.85) 94	(55.7 – 58,064) 100			
After delivery		BDE-209	–	–	432 (54.5 – 79,783) 100	–	–	–
6. Fromme et al. (2009)	Serum and diet — 17 Dust — 16	BDE-47	–	1.81 (0.23–6.44) 87	9.08 (1.71 – 255)	0.15 (0.06–1.37)[a]	–	ns
		BDE-99	–	0.75 (0.19–2.19) 77	12.5 (1.83 – 390)	0.18[F], 0.25[M] (0.06–2.17)[a]	–	ns
		BDE-153	–	2.37 (0.86–8.19) 94	2.69 (0.30 – 41.1)	0.05 (0.02–0.18)[a]	–	ns
		BDE-209	–	–	312 (29.7 – 1,460)	–	–	ns
7. Imm et al. (2009)	Serum — 24 Dust — 8	BDE-47	–	19.11*(–)100	520* (–)100	–	–	ns
		BDE-99	–	4.06*(–) 55	614* (–)97	–	–	ns
		BDE-153	–	4.53*(–) 11	73* (–) 84	–	–	ns
		BDE-209	–	b0.5*(–) 0	1389* (–) 100	–	–	ns
8. Johnson et al. (2010)	Serum — 11 Dust — 31	BDE-47	–	17 (bLOD-83)	390 (100–8627)	–	M, 0.81	0.002
			–	100	100	–	F, 0.80	0.002
		BDE-99	–	2.4 (bLOD-12)	427	–	M, 0.89	0.0001
			–	75	(79.3–12,967) 100	–	F, 0.69	0.01
		BDE-153	–	7.0 (1.3-154) 100	55.9 (13.2–1352) 100	–	M, 0.00F, 0.02	1.00N0.95
		BDE-209	–	b LOD (bLOD-6) 8	1,482 (425–32,366) 100	–	–	–
9. Karlsson et al. (2007)	Plasma and dust — 13	BDE-47	–	4.09 (b3.38–8.29) 60	25.9 (12.6–160) 100	–	–	–
		BDE-99	–	b 4.10 (all b4.10) 0	57.6 (23.9–194) 100	–	–	–
		BDE-153	–	2.20 (b0.988–3.86) 60	4.7 (2.39–7.10) 100	–	–	–
		BDE-209	–	11.5 (b5.54–17.4) 80	158 (43.9–1,560) 100	–	–	–
		∑ PBDE[h]	–	–	–	–	+ ve	–
10. Roosens et al. (2009)	Plasma, diet and dust — 9	BDE-153	–	–	–	–	0.16	0.08
		Σtri-hepta[b]	–	1.9 (0.9–7.2)	11.9 (5.3–69.7)	0.01 (b0.001–0.128)	–	ns
		BDE-209	–	–	106 (19.2–588)	0.139 (b0.04–7.750)	–	ns
11. Sahlstrom et al. (2014, 2015)	Serum — 12 Dust — 12	BDE-47	–	0.56 (b0.05–1.9) 100	21 (6.5–460) 96	–	–	ns
		BDE-99	–	0.078 (b0.049–0.49) 46	17 (b0.74–300) 93	–	–	ns
		BDE-153	–	0.95 (0.38–7.8) 100	1.9 (b0.27–77) 41	–	–	ns
		BDE-209	–	0.68 (0.32–9.5) 100	310 (143–310,000) 100	–	–	ns
12. Stapleton et al. (2012)	Serum, dust and handwipes — 11	BDE-47	–	23.3* (b3.0–350) 97	870 (55–24,720) 100	–	0.362	b0.01
		BDE-99	–	6.39* (b1.1–225) 99	919 (8–36,210) 100	–	0.280	b0.05
		BDE-153	–	5.34* (b0.5–83.1) 96	88 (7–3,407) 100	–	0.195	ns
		BDE-209	–	NA* (b6.0–63.8) 17	2,574 (441–76,130) 100	–	–	–
13. Stasinska et al. (2013, 2014)	Serum — 5 Dust — 33	BDE-47	–	3.96[f] (b0.92–191) 98	36.85 (2.55–391) 100	–		
		BDE-99	–	0.88[f] (b0.75–24.4) 58	56.75 (2.93–372) 100	–	Range 0.14–0.25	moderate N0.05
		BDE-153	–	2.26[f] (b0.55–65.4) 99	6.41 (bLOR–59.9) 100	–		
		BDE-209	–	–	415 (bLOR–82,200) 83	–	–	–
14. Toms et al. (2009)	Milk — 35 Dust — 22	BDE-47	4.10 (0.6-12) 100	–	56 (24-434) 100	–	–	ns
		BDE-99	0.85 (0.2-1.9) 100	–	87 (36-862) 100	–	–	ns
		BDE-153	1.20 (0.60-1.90) 100	–	7.4 (1.0-139) 100	–	–	ns

(continued on next page)

Table 2 (continued)

Study, measure of external exposure	Total number of PBDE congeners analysed	BDE congener	Milk ng/g lw	Blood ng/g lw	Dust ng/g dw	Diet ng/g ww	Correlations	
			Median (range) % detect				r	p
		BDE-209	0.50 (0.30-1.40) 50	–	291 (95-1,585) 100	–	–	ns
15. Watkins et al. (2011, 2012) office	Serum — 8 Dust and handwipes — 37	BDE-47	–	1.1* (b0.5-4.4) 80	697* (37 – 19,500) 100	–	0.22	0.25
		BDE-99	–	2.5* (b 1.9 - 45.9) 60	915* (b9.4 – 32,800) 97	–		
		BDE-153	–	5.0* (b0.5 - 173) 97	138* (11 – 5,970) 100	–		
Main living area		BDE-47	–	1.1* (b 0.5 - 4.4) 80	671* (b4.3 – 26,100) 97	–	0.42	0.02
		BDE-99	–	2.5* (b 1.9 - 45.9) 60	647* (b9.4 – 43,300) 94	–		
		BDE-153	–	5.0* (b0.5 - 173) 97	66* (b1.3 – 8930) 97	–		
Bedroom		BDE-47	–	1.1* (b 0.5 - 4.4) 80	454* (69 – 11,200) 100	–	0.49	0.008
		BDE-99	–	2.5* (b 1.9 - 45.9) 60	696* (119 – 7,410) 100	–		
		BDE-153	–	5.0* (b0.5 - 173) 97	59* (11 – 963) 100	–		
Vehicle		BDE-47	–	1.1* (b 0.5 - 4.4) 80	765* (38 – 19,000) 100	–	0.2	0.41
		BDE-99	–	2.5* (b 1.9 - 45.9) 60	1380* (55 – 25,800) 100	–		
		BDE-153	–	5.0* (b0.5 - 173) 97	125* (6.5 – 2,230) 100	–		
16. Whitehead et al. (2013, 2015)	Serum — 5 Dust — 22	BDE-47	–	35 (23–110)[d] 98	NA	–	0.45	0.001
		BDE-99	–	10 (6.5–25)[d] 100	NA	–	0.39	0.006
		BDE-153	–	8.9 (5.0–46)[d] 96	NA	–	0.1	0.5
17. Wu et al. (2007)	Milk — 12 Dust — 9	BDE-47	13.9 (2–126.6) 100	–	670 (240–14,610) 100	–	0.74	0.006
		BDE-99	2.4 (0.4–84.3) 100	–	1010 (290–14,800) 100	–	0.59	0.04
		BDE-153	3.0 (0.4–91.7) 100	–	110 (bLOD–560) 55	–	–	–
		∑ PBDE[g]	28.9 (3.9 - 261) 100	–	1,910 (590 - 34,400) 100	–	0.76	0.003
		BDE-209	bLOD (bLOD–10.9) 24	–	bLOD (bLOD–9,600) 45	–	i	i

ns = reported as not significant.
* = geometric mean reported.
NA = not available.
[a] = ng/kg body weight.
Σtri-hepta[b] = ΣBDE 28, 47, 99, 100, 153, 154, and 183
[c] = LOQ/√2.
[d] = 25th–90th percentile.
[e] = $\sum_8$PBDE.
[f] = estimated total lipids 5.54 g L^{-1}.
∑ PBDE[g] = ∑ BDE – 47, -66, – 85, -99, – 100, -138, – 153, and – 154.
∑ PBDE[h] = ∑ BDE -28, -47, -100, -99, -154 and -153.
[i] = insufficient samples.
LOR = Limit of Reporting.
Entries in bold indicate a significant correlation where p b/ = 0.05.

contribution to be 97% of the total exposure and Roosens et al. (2009) reported dietary contributions of 91% to 96% dependant on whether high or average dust ingestion rates were used to calculate the contribution of dust to the total PBDE exposure. Despite the high proportion of total exposure being from diet, neither study found correlation between PBDEs in duplicate diet and internal dose. In studies that gauged dietary exposure from food frequency questionnaires (FFQ), the most frequently reported associations with PBDE body burden were consumption of meat (Cequier et al., 2015; Imm et al., 2009; Sahlström et al., 2015; Wu et al., 2007), dairy products (Cequier et al., 2015; Wu et al., 2007) and fish (Cequier et al., 2015; Imm et al., 2009; Sahlström et al., 2015), suggesting that a vegan diet would help reduce exposure to PBDEs.

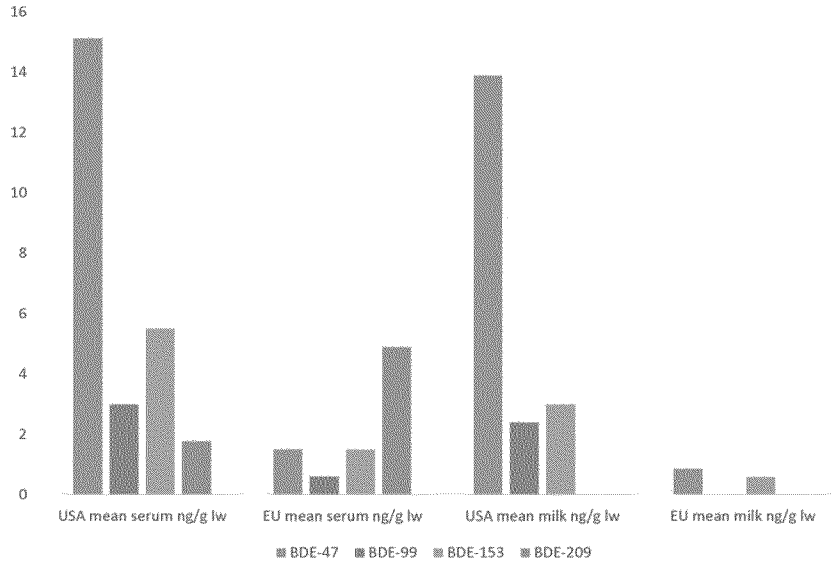

Fig. 2. Mean serum and breast milk PBDE concentrations for included studies for the USA and EU. Means are not directly comparable between studies due to differences in methods and sampling dates.

A number of demographic and anthropometric factors were highlighted as PBDE body burden predictors. Where studies were of women of reproductive age, body burden increased with age (Cequier et al., 2015; Stasinska et al., 2014). Studies including subjects aged 50 and over, as well as young adults, indicated exposure was higher for the younger age groups (Ali et al., 2014; Fromme et al., 2009; Imm et al., 2009). In the Stapleton et al. (2012) study of infants, their body burden also increased with age. Most studies with both male and female subjects did not report whether there was a difference in body burdens between sexes. Fromme et al. (2009) reported no significant difference and Stapleton et al. (2012) reported higher body burden in male toddlers. BDE-153 was found to be negatively associated with body mass index (BMI) (Cequier et al., 2015) and with parity (Stasinska et al., 2014). In the USA, children whose parents had a higher education level had lower PBDE body burdens except for BDE-153. Mothers' education level was positively associated with both length of time breastfeeding and infants' BDE-153 body burden (Stapleton et al., 2012).

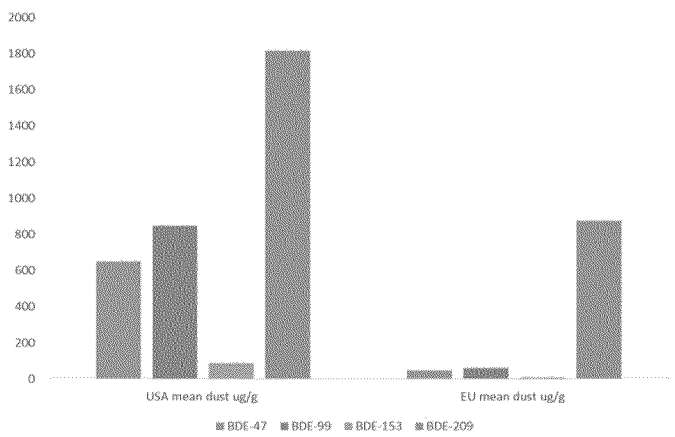

Fig. 3. Mean indoor dust PBDE concentrations for included studies for the USA and EU. Means are not directly comparable between studies due to differences in methods and sampling dates.

3.4. Quality of studies

We rated five of the 17 included studies as being of high quality (Bjorklund et al., 2012; Stapleton et al., 2012; Watkins et al., 2012; Whitehead et al., 2015; Wu et al., 2007), 11 of moderate quality (Ali et al., 2014; Cequier et al., 2015; Coakley et al., 2013; Frederiksen et al., 2010; Fromme et al., 2009; Imm et al., 2009; Johnson et al., 2010; Roosens et al., 2009; Sahlström et al., 2015; Stasinska et al., 2014; Toms et al., 2009) and one of low quality (Karlsson et al., 2007). Frequently observed shortcomings were inadequate sample size and limited demographics of subjects, uncertainties in exposure measurements, non-fasted blood samples, and lack of consideration for confounders.

4. Discussion

This systematic review aimed to assess the current international evidence of the association between PBDE concentrations in diet and indoor environments and diet and human body burden. A total of 17 studies met our inclusion criteria and reported paired human internal and external PBDE concentrations. Generalisation of findings from the individual settings was highly problematic due to the variation across and between studies. The small number of samples in each study limited their statistical power. Nevertheless, both the ubiquitous nature of the exposure and variation with place and time were clearly apparent.

Concentrations of the different PBDE congeners in different matrices, and correlations between them, were influenced by three key factors. Firstly there are regional use patterns and the time of study relative to the phase-out of PBDE technical products. PBDE body burdens in the USA are an order of magnitude higher than those within the EU. In regions where use restrictions of Penta- and Octa-BDE commercial products began earlier, and where their use was less widespread (EU), a different internal congener pattern emerged. Secondly, the human residency period and bioavailability varies greatly between congeners. As BDE-153 is the congener with the longest human half-life, its internal dose concentration increases with time relative to other congeners from the penta-BDE technical mix. Thirdly, the proximity and exposure pathways between the subjects and PBDE sources also vary. The closer the PBDE source is to a receptor and the more frequent and intense their contact is, the stronger their correlation. Exposure pathways

from soft furnishings and electronic items can be ingestion and inhalation of dust, inhalation of vapours and dermal contact. Ingestion and inhalation are the most direct routes of exposure and can be expected to have the strongest effects on body burden. People increase the amount of PBDE available for uptake by their use of the items, i.e. use of a computer keyboard, getting up and sitting down on soft furnishings and opening and closing curtains. Close physical contact between the human receptor and the treated item also provides opportunity for dermal contact. Coakley et al. (2013) suggested that the reason for such strong correlations between mattress dust and serum PBDEs was the amount of time spent in close proximity. Stapleton et al. (2012) hypothesised that their finding of very strong correlation between handwipes and serum for toddlers reflected the increased hand-to-mouth activity of young children and the high proportion of their time spent in the area where their dust samples and handwipes were taken. Bedroom and living room dusts demonstrated stronger correlations with body burden than (non PBDE related) work environments (Ali et al., 2014; Coakley et al., 2013; Watkins et al., 2012). Women on maternity leave and children, demonstrated stronger correlations with PBDEs in their home dust. Ali et al. (2014) suggested that the reason for the stronger correlation between dust and body burden in students than in electronic store workers had to do with the long periods the students spent in their rooms combined with less frequent cleaning.

The number of foam mattresses in a home, and numbers of flat screen TVs, the amount of time spent in the proximity of a working/switched-on TV have all shown associations with PBDE body burdens (Cequier et al., 2015; Dunn et al., 2010; Wu et al., 2007). However, these associations reduce as items containing PBDEs are replaced with new products containing different fire retardant chemicals. Therefore, using counts of domestic electronic equipment to determine PBDE exposure in the home may lead to measurement error (Allen et al., 2008). Environments that were cleaned/dusted more frequently also demonstrated lower correlation with body burden (Ali et al., 2014), indicating that more frequent cleaning may help reduce internal dose. As well as being a major exposure pathway for young children, hand-to-mouth behaviour may also be an important pathway for adults who bite their nails, smoke, or lick their fingers after eating snacks (Cequier et al., 2015). These are all potential opportunities for PBDE ingestion. Dermal absorption may be another pathway, so, not surprisingly, more frequent hand washing was associated with lower PBDE body burden (Watkins et al., 2012).

Dietary exposure to PBDEs may come from the food itself through bioaccumulation in the food chain, or in the case of farmed animal products, it is likely to be the result of contaminated animal feed. PBDE in food may also be the result of processing or packaging. Furthermore, deposition of dusts containing PBDEs onto food during processing or in the place of food consumption may also contribute. The two studies measuring PBDEs in seven day duplicate diets did not find significant correlations with body burdens, and this was interpreted as being the result of low exposure to PBDEs from dietary sources (Fromme et al., 2009; Roosens et al., 2009). Another problem with duplicate diets is that foods with significant PBDE concentrations are collected and mixed together with low or uncontaminated foods and are thereby diluted. Thus the PBDE concentration in the combined sample may fall below the LOQ. We argue that perhaps the average weekly duplicate diet was not a good indicator of non-fasted body burden. Diets analysed may also have consisted of food from such wide varieties of sources that patterns of exposure were not identifiable. It may be that strong congener correlations between diet and body burden only occur where a specific contaminated foodstuff is a regular/major part of the diet e.g. fish from a contaminated lake (Thomsen et al., 2008). Associations were also visible between frequency of consumption of food stuff with higher fat content such as dairy, meat and PBDE body burden (Cequier et al., 2015; Thomsen et al., 2010; Wu et al., 2007). In regions where penta-BDE use has been restricted for longer, penta- and octa-BDEs in body burden are hypothesised to result from diet and the higher brominated congeners from dust exposure (Sahlström et al., 2015).

The findings for the Penta-BDE technical mix congeners, BDE-153 and Deca-BDE technical mix/BDE-209 are sufficiently different to warrant separate summaries for each. Octa-BDE technical mix was primarily used in ABS plastics, often found in business equipment (e.g. fax machines and photocopiers). The included studies did not generally discuss findings in relation to the Octa-mix as it was used less widely in domestic products and therefore home exposure would be limited. Starting with Penta-BDE technical mix (major components BDEs-47, -99 -100 -153), there is strong evidence for dust as an exposure pathway. The Penta-mix, used with polyurethane foam (PUF) and electronics circuit boards (Betts, 2006; Hazrati and Harrad, 2006), has been used much more in North America than the rest of the world and this is reflected in the higher concentrations in home dust and body burdens. The human half-lives for the dominant penta-BDE components, i.e. BDEs-47, -99 and -100 (penta-BDE_3), were estimated to be short (approximately 1-3 years) in comparison to that of BDE-153 (a hexa-BDE) (approximately 12 years or more) (Geyer et al., 2004). Strongly significant correlations between $\sum$ penta-BDE_3 in dusts and body burden were seen in several studies. Intra-congener correlations indicated an ongoing source or sources of the technical mix.

Despite being present in the same technical PBDE mix, fewer significant correlations were reported for BDE-153 (Ali et al., 2014; Coakley et al., 2013). BDE-153 appears to be stored in human adipose tissue more effectively than other congeners, resulting in a longer human half-life. The influence of historic BDE-153 exposures on the internal dose makes the BDE-153 dose much higher than the present dust exposure would suggest. Johnson et al. (2010) reported strong correlation between cohabiting males and females except for BDE-153. BMI appears to be negatively correlated with BDE-153 suggesting that storage of BDE-153 in fat compartments results in dilution in persons with excess adipose tissue (Cequier et al., 2015; Fraser et al., 2009). Weight loss is suggested to increase chemical concentrations in fat tissues (Chevrier et al., 2000; Pelletier et al., 2003). The concentrated BDE-153 present in adipose fat compartments from historic exposures can be mobilised during weight loss. In a study of the milk of 83 women at three and 12 months postpartum, BDE-153 showed a significant increase over time (Daniels et al., 2010). A positive association was seen between length of breastfeeding time and toddlers serum concentrations of BDE-153, which was not seen for other PBDE congeners (Stapleton et al., 2012).

In regions where BDE-209 has been used in substantial quantities, there is no doubt of its ubiquity in dust, usually at much higher concentrations than other PBDEs. This is the result of its greater production volumes and usage. The particularly short residency time of BDE-209, low human bioaccessibility (Abdallah et al., 2012; Fang and Stapleton, 2014) and later use restrictions (if any) explain the differences in findings for BDE-209 from those of the Penta-BDE technical mix congeners. BDE-209 was commonly used for textile coatings and in electronics housings, connectors, plugs and switches. Where successfully measured in human milk, the proportion of BDE-209 of the total PBDE concentration varied from half the total PBDE body burden most recently (Coakley et al., 2013), to much smaller contributions (3.5% and b7% respectively in older studies (Toms et al., 2009; Wu et al., 2007). Although not measured in diet samples for studies included here, BDE-209 has been successfully measured in many foodstuffs (Fernandes et al., 2012). None of the included studies reporting BDE-209 data for both internal dose and dust found significant association between them. This lack of correlation may simply be the result of only recent advances in laboratory capacity for accurate measurement of BDE-209. BDE-209 is ubiquitous in most environments at high concentrations compared with other BDEs. During measurement, BDE-209 adsorbs to a much greater extent than other PBDEs, and is sometimes not recorded. Use of a ^{13}C labelled BDE-209 internal standard allows considerably greater reliability of determination.

So which BDE congener can be expected to be the most toxic to humans? The US-EPA (2010) developed reference dose values (RfD) (estimates of daily oral dose, for a lifetime, likely to be without appreciable risk of deleterious effect) for key PBDE congeners. BDEs-47 and -99 were considered the most potent, both with RfDs of 0.1 μg/kg/day, then BDE-153 at 0.2 μg/kg/day and BDE-209 considerably less so at 7.0 μg/kg/day. EFSA (2011) used a margin of exposure (MoE) approach (the ratio between the safe dose and the estimate of exposure for a population). They concluded that, in Europe, BDE-47, -153 and -209 did not raise health concerns, but that the MoE for BDE-99 in children 1–3 years old was estimated to be below the acceptable MoE of 2.5.

The answer to the question of whether indoor dust exposure or diet is the primary pathway for non-occupational human exposure to PBDE is time- and site-specific. For penta- and octa-BDEs, dietary exposure appears to be similar in both the USA and mainland Europe, so the higher body burdens measured in the USA must be attributable to the higher dust loadings (Frederiksen et al., 2009b). In the two included European studies measuring both dust and dietary exposure, diet was reported to provide over 90% of body burden, despite low dietary PBDE concentrations (Fromme et al., 2009; Roosens et al., 2009). When PBDE sources in the home and workplace are phased out, the proportion of body burden from dietary exposure can be expected to increase for the PBDEs with longer biological half-lives that are found in the food chain, but not for BDE-209.

4.1. Strengths and limitations of included studies

Only one study included their study design (cross sectional and convenience) (Watkins et al., 2012). A general shortcoming was that all studies were from single countries, so differences between regulatory regions were not explored. Extrapolation of participant bio-data to wider populations may be limited given the homogeneous nature of several participant groups. Most of the studies were for a single time point which could be misleading. However, where dust sampling was repeated, the congener proportions were generally found to be similar although loading could change (Frederiksen et al., 2010). The high costs of PBDE analysis, recruitment of study subjects and sample collection may be the reason that many studies are conducted with limited sample numbers.

With higher lipid content than blood, milk samples are a more accurate representation of body burden, although clearly the population for which this observation is possible is limited. Blood has low lipid content, typically e.g. 0.3% to 0.9% (Bramwell et al., 2014), and as PBDEs are stored in blood lipid, analytical laboratory accuracy improves with sample volume. Studies on POPs in human blood generally recommend that fasted samples are taken in order to avoid the influence of recently consumed foods that may give rises to temporary changes in blood levels (Fierens et al., 2003; Nakamoto et al., 2013). However, only one study reported collecting a fasted blood sample (Ali et al., 2014). Internal dose results are usually normalised on a lipid basis according to convention although there is some debate as to whether or not different PBDE congeners in serum are strongly correlated with lipid content (Hakk et al., 2002; Verreault et al., 2007). Most included studies measured lipid in their samples in order to lipid normalise their blood PBDE concentrations, although one did not (Stasinska et al., 2014). The accuracy of blood lipid measurement can also be a large source of measurement uncertainty, as serum lipids are commonly determined by clinical enzymatic methods and approaches to calculate the total lipid content vary between laboratories.

A strength for a number of included studies was that they collected dust samples from a specified floor area and some for a specified time, depending on floor cover, making their results comparable (Ali et al., 2014; Coakley et al., 2013; Roosens et al., 2009). This technique also appeared to give stronger correlations. The study by Coakley et al. (2013) stood out for having so many significant correlations for components of the penta-, octa-, and deca-BDE formulations. Twenty-nine significant correlations (both inter and intra congener) were reported between living room floor dust and milk and 35 between mattress dust and milk. The strongest of these were correlations between mattress dust and milk. These findings highlighted the complexity of inter congener and inter matrix relationships. Correlations between body burden and mattress dust seem plausible given the amount of time spent in close proximity. Correlation between home or office characteristics or contents is limited (Allen et al., 2008) and will become more so as the products containing PBDEs are replaced.

Collection of dietary information is particularly challenging. Study participants may alter their diet when being observed. When duplicate diets are collected by the participant, food items consumed may not always be replicated in the collection vessel. Another issue with duplicate diets is that they reflect only a brief window of time, whereas POPs such as PBDEs, long term dietary habits are also likely to be reflected by body burden. The proportion of influence from short, median and long term dietary exposure is complex including factors such as fasted state and current loss or gain of body fat. FFQs are one method of assessing long-term dietary exposure, however they rely on the participant's memory and estimation of portion sizes (if included). Studies using validated or standard FFQs have found they may not be sufficiently detailed to identify specific PBDE sources (Dunn et al., 2010). Food recall (FR) questionnaires, such as 24 hour FR, provide greater accuracy. New technology may lead to more accurate dietary assessment. Computer programs and smart phone applications are now able to identify foods and approximate weights from photographs and allow less burdensome multiple-pass 24-hour recall e.g. Intake24 (Foster et al., 2014).

Although all but two studies reported BDE-209 concentrations in dust samples (Watkins et al., 2012; Whitehead et al., 2013), only eight of the studies were able to report measurements of BDE-209 in either blood or breast milk. Furthermore, only four studies reported results of correlation analysis for BDE-209. Recoveries of BDE-209 are reported to be considerably higher from dust than serum (Van den Eede et al., 2012; Xie et al., 2010). Sample lipid content has been suggested to negatively influence the recovery of the more highly brominated halogenated flame retardants having high K_{ow} (N9.4) (Cequier et al., 2014b). As such, internal standards with similar K_{ow} (i.e. similar recovery) are necessary to prevent underestimation of results, even with well optimised extraction procedures. ^{13}C BDE-209 standard recoveries were rarely reported in the included studies: 13–39% (Karlsson et al., 2007) and mean 64% (Sahlstrom et al., 2014). Frederiksen et al. (2009a) reported the recovery to be low and leading to large uncertainty. Analytical difficulties and measurement uncertainties for BDE-209 were clearly a common limitation.

Only a few studies reported all correlations for all congeners measured. Many presented only a few in the text or stated that no significant correlations were found. If all correlations had been presented, a meta-analysis may have been feasible.

Using the adapted HONEESS scheme, only one study was found to be of low quality (Karlsson et al., 2007). The study design and participants were not described, there were only five participants, and laboratory quality control measures did not include standard reference materials (SRMs) or inter-laboratory studies. This was, however, the earliest of the included studies.

4.2. Confounders

Exposure concentrations varied widely between the USA and the rest of the world, and between California and the rest of the USA. There were also differences between urban and rural regions. A country or state's flame retardant regulations affect volumes of use, therefore differences in dates of phase out are limitations for inter-study comparisons. The introduction of multiple replacement flame retardant chemicals for PBDE is a confounder for using numbers of flame retardant containing items in the home as a predictor of dust and serum PBDE loading. Studies with longer time lapse between collection of internal dose and exposure

samples (or vice versa) could find confounders being introduced if some everyday exposures had changed. Diet varies between seasons, regions and countries resulting in limitations for inter-study comparison; e.g. populations with high proportions of fish in their diet reflect this in their internal PBDE exposure patterns (Sahlström et al., 2015).

Age of participants also influences body burden. Exposures in infancy (and therefore internal dose) appear to be greater than those for adults. Initially sharing the mother's adult internal dose in utero, during breast feeding the primary exposure pathway is diet, changing to a greater dust exposure which decreases as hand to mouth behaviours reduce (Rose et al., 2010). The 2003–4 American 'National Health and Nutrition Examination Survey' NHANES cohort (n = 1892) found younger adults had higher PBDE levels than the other adult age groups in the study (Fraser et al., 2009). There is evidence that BMI may impact on PBDE body burden, particularly for BDE-153. Fraser et al. (2009) reported that PBDEs tended to increase with decreasing BMI for the NHANES study with highest concentrations measured in the underweight, although this remained significant for only BDE-153 after adjustment for covariates age and race/ethnicity. Although Fromme et al. (2009) (n = 61) found no significant differences in internal dose between male and female adults, Stapleton et al. (2012) found male toddlers to have higher body burdens than females and body burdens were found to be highest among males for the NHANES 2003-4 cohort (Fraser et al., 2009). Depuration of PBDEs in women from pregnancy and lactation period could be a contributing factor in adults (particularly for BDE-153), but for toddlers, differences in activity or other reason/s must have a role. Consistency of postpartum timing of milk collection, time of day, hind milk or foremilk, or complete expression on milk PBDE concentrations could help provide clearer evidence of the depuration effects of lactation (Daniels et al., 2010; Dunn et al., 2010). However, differences in pre-maternity BMI, maternal weight gain, exercise and weight loss will still limit the findings.

Where single time point samples are taken, timing of internal and external exposure measurements may result in confounders. Unusual dietary or dust exposure may be reflected in blood or milk which may not be evident in dust or diet samples from regular external exposure samples or questionnaire. Taking a fasted sample should reduce impact of immediate exposures although it is not ethical/ advisable to request for milk samples or children's blood samples.

Lower income and educational attainment, are indicated as predictors of raised BDE-47 in the USA (Fraser et al., 2009; Rose et al., 2010; Stapleton et al., 2012). This might be the result of different building materials and furniture quality. However, on further investigation, house dust concentrations and condition of foam furniture did not explain disparity of serum penta-BDEs by income (Whitehead et al., 2015; Zota et al., 2008).

Where samples of only dust or only diet were measured, the lack of data on other PBDE sources was reported as a limitation (Stapleton et al., 2012). However, Wu et al. (2007) reported that dust and diet were independent predictors of PBDE body burden. Future studies are encouraged to consider these, and other, factors as possible confounders, as studies included in this review did not have sufficient statistical power to rule them out.

4.3. Strengths and limitations of the review

To the authors' knowledge, this is the first review of correlations between external exposure and human internal dose of PBDEs. An important strength of this study is the adherence to standard systematic review methods. We used validated systematic review methods, exhaustive search techniques, specified inclusion criteria and used the PRISMA checklist to guide reporting essential information from the included studies. A review of current evidence is now timely as sufficient studies have been reported since Karlsson et al. (2007) published their first peer reviewed investigation into correlations between internal and external PBDE.

A major limitation of this review was one person data extraction for the most part. There were several methodological limitations. The exclusion of non-English publications means that potentially relevant articles may have been missed. The exclusion of non-peer reviewed studies excluded an early study of matched milk and dust (Sharp and Lunder, 2004) available only via internet. We did not attempt to search for 'grey literature' which may contain smaller null-result studies that were not accepted for publication. Lastly, the results are limited by the conduct and reporting of the studies from which the data were extracted.

5. Recommendations and conclusions

Our review ascertained that the question of whether dust or diet is the primary human exposure to PBDE may not be possible to answer. To adequately respond to the question would require concurrent international longitudinal investigations, with sufficient statistical power to address the confounders mentioned in Section 4, using consistent methods for sample collection, analytical and statistical analysis and reporting. Different PBDE usage and exposure regions such as North America, mainland EU, the Indian subcontinent and Australasia as well as regions not represented in this review, particularly electronics recycling areas, and historically heavy users such as the UK and Japan should be included.

Technical developments of faster, cheaper extraction of PBDE from biological samples would allow studies to include more subjects. The use of handwipes as a representation of external non-dietary exposure looks promising and should be explored further. As PBDEs, in many instances, have already been replaced by alternative halogenated or organophosphate flame retardants, these should be included where possible in future monitoring. Inclusion of measurements for BDE-209 for all matrices is essential. Reporting using STROBE guidelines would assist inter-study comparability. A considerable body of new research has been undertaken since the 2009 review of human internal and external PBDE exposures (Frederiksen et al., 2009b). An update of this review, including PBDE replacement chemicals may be able to show effects of restrictions on PBDE by replacement of other chemicals.

Our review concluded that there were three key factors influencing the correlation between external and internal PBDE exposure, and three distinct congener behaviours were apparent. Time of study relative to phase-out of PBDE technical products for the country of study, half-life of individual congeners in the human body, and time spent in the location of the source and proximity between PBDE source and study subject were all key factors. Penta-BDE_3 (BDEs-47, -99 and -100), BDE-153 and BDE-209 had distinct exposure patterns. Although penta-BDE_3 and BDE-153 are found in the same technical mix, penta-BDE_3 had much stronger internal - external correlations. The longer human half-life of BDE-153 resulted in an increased proportion of total PBDE body burden which also reflected historic exposures. BDE-209 required a current exposure source to create a significant internal correlation. Because PBDE loading in dust is influenced by discrete sources of PBDE technical mix within the indoor environment, correlations with internal dose were more likely to be detected. Dietary PBDE loading may be from more diffuse sources and dietary exposure is less consistent, so correlation with internal dose is less likely.

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Appendix A. Supplementary data

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Associations between human external and internal exposure to polybrominated diphenyl ether) flame retardants: A systematic review

Supplementary information

1) Search Strategy and Terms

The study will be conducted according to the PRISMA statement.

Data sources: Four electronic databases (Pubmed, EMBASE, Web of Science, Scopus) searched with the assistance of I.H.S. Information Specialist.

PBDE=polybrominated diphenyl ethers

Search terms:

EMBASE 1974 to 2015 week 4
PBDE exposure in humans, full text, English language:

1.($bde OR pbde OR pbdes OR (polybrominated and ('diphenyl' de OR diphenyl) and ('ethers' de OR ethers))) AND
2.(serum$ OR plasma$ OR blood$ or milk$ OR internal OR 'body burden'$ OR exposure$) AND
3. (diet$ OR food$ OR dust$ OR air$ OR indoor$ OR environment$ OR exposure$ OR factor$ OR lifestyle$ OR source$ OR behav$) AND
4. (match$ OR pair$ OR relation$ OR association$ OR evidence$ OR predict$) AND

($bde OR pbde OR pbdes OR (polybrominated and ('diphenyl' de OR diphenyl) and ('ethers' de OR ethers))) AND (serum$ OR plasma$ OR blood$ or milk$ OR internal OR body burden$ OR exposure$) AND (diet$ OR food$ OR dust$ OR air$ OR indoor$ OR environment$ OR exposure$ OR factor$ OR lifestyle$ OR source$ OR behav$) AND (match$ OR pair$ OR relation$ OR association$ OR evidence$ OR predict$).ti,ab

Searched for in titles, keywords and abstracts

Additional searching:
Reference list review
Any article deemed suitable by reviewers is included for closer examination.

Inclusion/exclusion criteria
Inclusion criteria:
Studies were included if they were published in a peer-reviewed journal, written in English and reported investigation of correlation between paired human internal (blood and milk only) and external (dust and diet only) PBDE concentrations.
Papers were excluded in internal and external measurements were not paired, or if the external measurement investigated was purely occupational, from a hobby or a specific type of food.

2) PRISMA Checklist of items for inclusion when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4

Section/topic	#	Checklist item	Reported on page #
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	SI1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Tables 1 & 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 & 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	17 & 21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22